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09/807,579	11/28/2001	Jean Rommelaere	03528.0127.NPUS00	2091

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EXAMINER	
MOSHER, MARY	
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1648	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,579	Applicant(s) Rommelaere et al
	Examiner Mosher	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing for several reasons. First, the claim is drawn to a parvovirus vector "having parvovirus DNA excisable from the vector DNA in a parvovirus-permissive cell". Does this mean that the claimed vector is something other than a parvovirus, the vector contains at least a parvovirus left terminus, the left terminus contains a parvo minimal origin of replication, and the parvovirus DNA can be spontaneously excised from the vector in a parvo-permissive cell? Second, the term "minimal origin of replication" appears to mean different things to different workers in the parvovirus art. The specification refers to Cotmore et al (1994, cited in IDS) for a definition, which is an improper incorporation by reference of material that is essential for understanding and practicing the invention. Even the Cotmore publication does not contain a clear definition of "minimal origin of replication". The specification, page 3, states that a minimal parvovirus origin of replication comprises the consensus sequence of an NS1-nicking site, preferably CTWWTCA (where W is any nucleotide). But Cotmore states that both ends of the MVM genome contain origins of replication, and that both contain the sequence CTWWTCA, see page 4147 under "Mapping the in vitro nick site." On the other hand, Ward et al (Virology 209:692-5, 1995) uses the phrase "minimal origin of replication" to refer to a sequence without a

nicking site. Therefore, it is not clear what is required for a "minimal origin of replication" in the claimed vector. Third, Christensen et al (Journal of Virology 75:7009-7017, 2001, not available as prior art) is cited as evidence that parvoviruses such as MVM normally have a minimal origin of replication at the left end. It is apparent that applicants intend to require some change from the normal MVM terminal structure, but it is totally unclear what this change involves. The working examples do not provide any illumination on this point, as the discussion of restriction digestion and ligation of named molecules does not communicate how the manipulations relate to the purposes set forth in the specification. Therefore it is very unclear what structure is required in the claimed vectors.

In claim 2, it is not clear what is meant by "internal replication sequences", as this phrase does not appear to be defined anywhere in the specification (except possibly by another improper incorporation by reference); no ordinary meaning is apparent.

In claim 3, the claim refers to "an NS1 nicking site". How does this apply to parvoviruses which do not have any protein designated "NS1", such as adeno-associated virus? Does the claim require a site that can be nicked by MVM NS1, or does the claim encompass sites nicked by AAV rep68 for example? In the interest of compact prosecution, this recitation has been interpreted broadly as a nick site for the parvoviral replicase protein, whether or not the protein is designated as NS1 in that parvovirus.

Claim 21 is indefinite, because it recites a nucleotide sequence without a SEQ ID number. Please note, if this sequence recitation is not already included in the Sequence Listing, a replacement Sequence Listing will be required.

Claims 19-20 provide for the use of a parvovirus vector for gene therapy, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As discussed above for claim 1, it is very unclear what structural elements are required in the claimed products. The claims require a left terminus with a minimal origin of replication, and it appears from the specification that some manipulation of a terminal sequence is intended, but publications such as Christensen (co-authored by one of the inventors) indicate that a left-end minimal origin of replication is normally present in a parvovirus such as MVM. Therefore it is not clear what is actually required in the claimed product. Without a clear understanding of what the claimed product actually is, one skilled in the art cannot possibly make the claimed product. Therefore, because of this confusion, it is concluded that the specification does not enable one skilled in the art to make the claimed invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims are broadly drawn to gene therapy using a parvovirus vector. The recent article by Kaiser is cited as illustrative of the state of the art of gene therapy, several years later than the effective filing date; only one "clear success in gene therapy" is known, which did not involve a parvoviral vector. Therefore, at the time the invention was made, successful gene therapy using a parvoviral vector was not a matter of routine for practitioners of the art. The specification provides little guidance and no working examples for gene therapy. Considering the state of the art, the limited guidance, the absence of working examples, and the quantity of research required to succeed in gene therapy, it is concluded that undue experimentation would be required to practice the invention as claimed.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Samulski et al (Journal of Virology 61:3096-3101, 1987). Samulski teaches a plasmid psub201, containing a parvovirus genome, where the right terminus sequence has been substituted for the left terminus sequence, see page 3907. The parvovirus is able to replicate in permissive cells without being first excised from the plasmid, see page 3908, particularly Fig. 2A and the accompanying text. Although the reference is silent upon the presence of a nicking site, this appears to be an inherent feature of the parvovirus right terminus sequence, see as evidence the abstract by Ward et al (Journal of Virology 68:6029-37, 1994).

Claims 1-4, 9, 14, 15, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Shenk et al 5,436,146. Shenk teaches the plasmid psub201, which is identical to the plasmid taught by Samulski above. In addition, Shenk teaches replacement of the parvoviral coding

sequence with exogenous DNA, and its packaging into particles, thereby meeting the claim limitations. See columns 16-18.

Claims 1-4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Srivastava et al (PNAS 86:8076-8082, 1989). Srivastava teaches a construct combining the termini of psub201 with DNA from another parvovirus, thereby meeting the claim limitations.

Claims 1-6, 9, 14, 15, 18, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Maxwell et al 5,585,254. Maxwell teaches autonomous parvovirus vectors with the parvovirus left and right termini, including minute virus of mice and bovine parvovirus, see claims 1 and 9. Metcalf et al (Journal of Virology 64:5485-90, 1990) is cited as evidence that the bovine parvovirus left terminus contains a minimal origin of replication. Therefore, the bovine parvovirus embodiment taught by Maxwell necessarily and inherently possesses each and every feature recited in claims 1-4, 9, 15, and 18. In addition, if MVM normally has a left-end minimal origin of replication (as evidenced by Christensen et al), then the MVM embodiments taught by Maxwell also necessarily and inherently possess each and every feature recited in claims 1-6, 9, 15, 18, and 21.

Claims 1-6 and 21 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Tam et al (Virology 193, 812-824, 1993). Tam teaches plasmid vectors containing MVM parvovirus termini. Tam teaches MVM a construct with "left" sequence at both left and right termini, and a construct with "right" sequence at both left and right termini. See Figure 1. Since both types of constructs can replicate, they apparently both contain minimal origins of replication, and therefore

meet each and every limitation of the claims. The RR construct also includes nucleotides 4431-4579 and 4579-4662, which are cited in the specification as examples of the undefined "internal replication sequences", thereby clearly meeting the limitations of claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-12, 15, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki et al 6,221,646. Dwarki teaches a method for producing recombinant AAV. Dwarki suggests psub201 as a suitable rAAV vector, see column 6, lines 25-26, and teaches insertion of coding sequences for cytokines and chemokines in the vector, see column 9, lines 37-51, and suggests use of the rAAV in gene therapy, see column 1, lines 44-51. It would have been within

the ordinary skill of the art to combine the suggested vector with the suggested insert, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki et al 6,221,646 as applied to claims 9-12, 15, 18, and 19 above, and further in view of Williams et al. As discussed above, Dwarki teaches rAAV vectors encoding chemokines. Dwarki differs from this claim in that Dwarki does not specifically mention MCP-1. however, Williams teaches that MCP-1 is a chemokine, see column 2, lines 21-24. It would have been within the ordinary skill of the art to express this additional chemokine from an rAAV vector, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Claims 10, 11, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shenk et al 5,436,146 as applied to claims 1-4, 9, 14, 15, 17, and 18 above, and further in view of Kurtzman et al 5,952,221. As discussed above, Shenk teaches rAAV vectors with the characteristics recited in the parent claims. Shenk does not teach use of the rAAV in therapy of diseases such as tumor diseases. However, Kurtzman teaches successful treatment of tumor diseases using rAAV expressing a toxin. It would have been within the ordinary skill of the art to use the conventional psub201 rAAV vector in the same manner as the other rAAV vectors of Kurtzman, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shenk as applied to claims et al 5,436,146 as applied to claims 1-4, 9, 14, 15, 17, and 18 above, and further in view of Chiorini et al 5,693,531. This claim differs from Shenk in that it requires an SV40 vector to supply the AAV capsid proteins. Chiorini teaches increased production of rAAV particles by using an SV40 vector, because of the ability to induce high-copy replication of the SV40 vector. It would have been within the ordinary skill of the art to substitute the SV40 cap vector for the cap vector used by Shenk, for the purpose of improving virion production, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Claim 8 is seen as free of the art, as the prior art does not appear to provide motivation to combine an MVM minimal origin of replication (however it is defined) with H-1 parvovirus DNA.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is (703) 308-2926. The examiner can normally be reached on Monday -Thursday and alternate Fridays from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is now (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

March 6, 2003

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600